A Novel Model of Fetal Spinal Cord Exposure Allowing for Long-Term Postnatal Survival.

Journal: Fetal Diagn Ther

Publication Year: 2021

Authors: Sarah C Stokes, Jordan E Jackson, Christina M Theodorou, Christopher D Pivetti, Priyadarsini Kumar, Kaeli J Yamashiro, Aijun Wang, Diana L Farmer

PubMed link: 34111873

Funding Grants: Placental Mesenchymal Stem Cell Augmentation of Fetal Myelomeningocele Repair

Public Summary:
Myelomeningocele (MMC), the most severe form of spina bifida, is a birth defect resulting from the incomplete closure of the neural tube during fetal development. This birth defect causes varying degrees of lower body paralysis, disabilities, and bladder, bowel, and sexual dysfunction. A previous study, the Management of Myelomeningocele Study (MOMS), established fetal surgical repair of the MMC defect as the current standard of care treatment. However, despite the benefits demonstrated in this trial, only 55% of patients who underwent fetal surgical repair were able to walk at a 30-month follow up. Hence, there remains an unmet clinical need, and researchers are currently reworking the fetal MMC repair by evaluating novel therapies in various animal models. Fetal MMC animal models are designed based on how the spinal cord is hypothesized to be damaged, via a 2-hit hypothesis of injury. The first hit results from the fetus' inability to properly close the neural tube during fetal development, thus leaving the delicate spinal cord exposed to the intrauterine environment. The second hit results from the prolonged exposure of the spinal cord to the fetal environment, allowing the spinal cord to accrue additional damage from the amniotic fluid and direct trauma, thus causing the MMC defect. The fetal lamb MMC model is a commonly used animal model used for MMC studies due to the large fetal size, long duration of gestation, and low rate of preterm labor. In fetal lamb models, MMC defects are created by surgically exposing the spinal cord to the fetal environment for a period of time before repairing it. However, given the innate ability of lamb fetuses to heal wounds, a wound larger than a naturally occurring MMC defect needs to be created for our proper comparison to human birth defects. Unfortunately, this also increases the severity associated with fetal sheep models of MMC and has created challenges for long-term survival of lambs. We aimed to develop a fetal sheep surgical spinal exposure model which would result in the ability to survive lambs for a long time with normal motor function, and as such, would be suitable to test the long-term safety of novel therapeutic products. The model described here allows for direct application of an experimental product to the spinal cord of the fetal lamb and allows for survival of the lambs to at least 3 months. The new fetal sheep spinal cord exposure model consists of fetal surgery with the removal of two vertebrae, spinal cord exposure, and an application of a therapeutic product directly to the spinal cord. Lambs that underwent this fetal surgery survived to the planned study endpoint of 3 months. They also did not develop worsening motor function. Therefore, this model allows for a direct application of experimental products to the spinal cord without the clinical symptoms associated with the previously used fetal sheep MMC models. Longer term survival may be possible and remains to be studied.

Scientific Abstract:
BACKGROUND: The inherent morbidity associated with fetal ovine models of myelomeningocele (MMC) has created challenges for long-term survival of lambs. We aimed to develop a fetal ovine surgical spinal exposure model which could be used to evaluate long-term safety after direct spinal cord application of novel therapeutics for augmentation of in utero MMC repair. METHODS: At gestational age (GA) 100-106, fetal lambs underwent surgical intervention. Laminectomy of L5-L6 was performed, dura was removed, and an experimental product was directly applied to the spinal cord. Paraspinal muscles and skin were closed and the fetus was returned to the uterus. Lambs were delivered via cesarean section at GA 140-142. Lambs were survived for 3 months with regular evaluation of motor function by the sheep locomotor rating scale. Spinal angulation was evaluated by magnetic resonance imaging at 2 weeks and 3 months. RESULTS: Five fetal surgical intervention lambs and 6 control lambs who did not undergo surgical intervention were included. All lambs survived to the study endpoint of 3 months. No lambs had motor function abnormalities or increased spinal angulation. CONCLUSION: This model allows for long-term survival after fetal spinal cord exposure with product application directly onto the spinal cord.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/novel-model-fetal-spinal-cord-exposure-allowing-long-term-postnatal-survival